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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) 9-Fluoroprostaglandin Derivatives, Process for Their Production and Their Pharmaceutical Use

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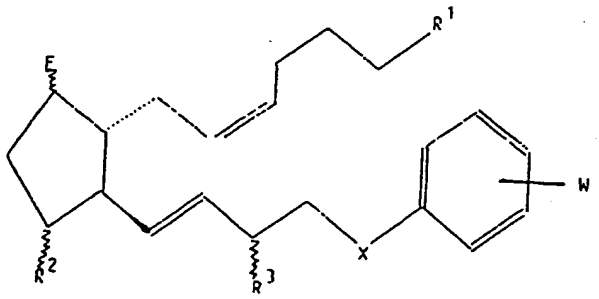
9-Fluoroprostaglandin Derivatives, Process for their Production and their Pharmaceutical Use

The invention relates to 9-fluoroprostaglandin derivatives, process for their production as well as their use as auxiliary agents for pharmacological analyses and as pharmaceutical agents.

It has been found, surprisingly, that chemically and metabolically stable prostaglandin analogs, whose pharmacological properties are comparable to those of unstable thromboxane A_2(TXA_2) or PGH_2, are obtained by the introduction of a fluorine atom in 9 position in connection with an aromatic substituent in 17 position.

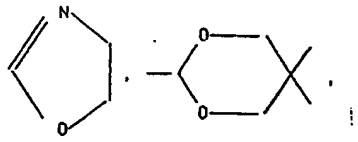
The compounds of this invention therefore are suitable as auxiliary agents for pharmacological characterizations as well as for selective treatment of diseases, which are attributable to a deficiency in endogenous TXA_2/PGH_2.

The invention relates to 9-fluoroprostaglandin derivatives of formula I,



(I),

in which

R^1 can be ---  , $COOR^4$, in which R^4

can mean hydrogen

or a C_1-C_{10} alkyl radical optionally substituted by halogen, phenyl, C_1-C_4 alkoxy or di-(C_1-C_4) alkylamino, a C_3-C_{10} cycloalkyl radical, a C_7-C_{16} aralkyl radical, a phenacyl radical substituted by W, a C_6-C_{12} aryl radical or a 5- or 6-member heterocyclic radical with at least one N, O or S atom, or R^1 can be a $CONHR^5$ radical with R^5 meaning hydrogen, C_1-C_{10} alkanoyl or C_1-C_{10} alkanesulfonyl,

R^2 and R^3 each mean a hydrogen atom or a free or functionally modified hydroxy group, and the OH group can be respectively in alpha- or beta-position,

X means a CH_2 group, an O or S atom,

W means hydrogen, $-OR^6$, halogen, -CN-, $-NO_2$, trifluoromethyl or $COOR^6$,

R^6 can be hydrogen, C_1-C_{10} alkyl, C_6-C_{12} aryl or C_7-C_{16} aralkyl substituted by halogen, and, if R^4 means hydrogen, their salts with physiologically compatible bases, as well as the alpha-, beta- or gamma-cyclodextrin clathrates, as well as the compounds of formula I encapsulated with liposomes.

The definition of 5- or 6-membered heterocyclic radical relates to heterocycles, which contain at least one heteroatom,

preferably nitrogen, oxygen or sulfur. For example, there can be mentioned 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl.

As alkyl groups R^4 and R^6, straight-chain or branched-chain alkyl groups with 1-10 C atoms, such as, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, isopentyl, neopentyl, heptyl, hexyl, decyl, are to be considered.

Alkyl groups R^4 and R^6 can be substituted by halogen atoms, hydroxy groups, C_1-C_4 alkoxy groups, C_6-C_{12} aryl groups, which can be substituted by halogen, di-(C_1-C_4)-alkylamines and tri-(C_1-C_4)-alkylammonium. Those alkyl groups which are singly substituted are preferred.

As substituents, for example, there can be mentioned fluorine, chlorine or bromine atoms, phenyl, dimethylamino, diethylamino, methoxy, ethoxy.

As preferred alkyl groups R^4 and R^6, those with 1-4 C atoms, such as, for example, methyl, ethyl, propyl, isobutyl, butyl, can be mentioned.

As aryl groups R^4 and R^6, for example, phenyl, diphenyl, 1-naphthyl and 2-naphthyl, which can be substituted by 1-3 halogen atoms, a phenyl group, 1-3 alkyl groups each with 1-4 C atoms, a chloromethyl group, fluoromethyl group, carboxyl group, C_1-C_4 alkoxy group or hydroxy group, are suitable. The substitution in 3- and 4-position on the phenyl ring is preferred, for example, by fluorine, chlorine, C_1-C_4 alkoxy or trifluoromethyl or in 4-position by hydroxy.

Cycloalkyl groups R^4 can contain 3-10 carbon atoms, preferably 3-6 carbon atoms, in the ring. The rings can be substituted by alkyl groups with 1-4 carbon atoms. For example, there can be mentioned cyclopropyl, cyclobutyl, cyclopentyl, methylcyclopentyl, methylcyclohexyl.

Especially preferred cycloalkyl groups are cyclopentyl and cyclohexyl.

As C_7-C_{16} aralkyls, the following radicals are meant: phenyl-substituted alkyl radicals (straight-chain and branched) with 1-10 C atoms, such as, for example, benzyl, phenylmethyl, alpha-phenylethyl, 3-phenylpropyl, etc. But 1- or 2-naphthyl with a suitably shorter alkyl chain are also suitable as Ar.

The alkyl groups or alkoxy groups with 1-4 C atoms mentioned as substituents are to be straight-chain or branched-chain.

The hydroxy groups in R^2 and R^3 can be functionally modified, for example, by etherification or esterification, and the free or modified hydroxy groups can be in alpha- or beta-position, and free hydroxy groups are preferred.

As ether and acyl radicals, the radicals known to one skilled in the art are suitable. Easily cleavable ether radicals, such as, for example, the tetrahydropyranyl radical, tetrahydrofuranyl radical, tert-butyldimethylsilyl radical, tert-butyldiphenylsilyl radical, tribenzylsilyl radical, are preferred. As acyl radicals, for example, acetyl, propionyl, butyryl, benzoyl are suitable.

Halogen in the definitions for R^4, R^6 and W means fluorine, chlorine and bromine.

Radicals "C_1-C_{10} alkanoyl" or "C_1-C_{10}-alkanesulfonyl" for R^5 correspond to the already mentioned alkyl groups of the same length with the difference that they are bound on a carboxyl group. C_1-C_4 alkanoyl or C_1-C_4 alkanesulfonyl are preferred.

Inorganic and organic bases are suitable for salt formation with the free acids (R^4 = H), as they are known to one skilled in the art for forming physiologically compatible salts. For example, there can be mentioned: alkali hydroxides, such as sodium hydroxide or potassium hydroxide, alkaline earth hydroxides, such as calcium hydroxide, ammonia, amines, such as ethanolamine, diethanolamine, triethanolamine, n-methylglucamine, morpholine, tris-(hydroxymethyl)methylamine, etc.

Preferred compounds of formula I are compounds in which

R^1 means the group $COOR^4$,

R^2 means hydrogen or hydroxyl,

R^3 means hydrogen or hydroxyl,

R^4 means hydrogen or C_1-C_6 alkyl,

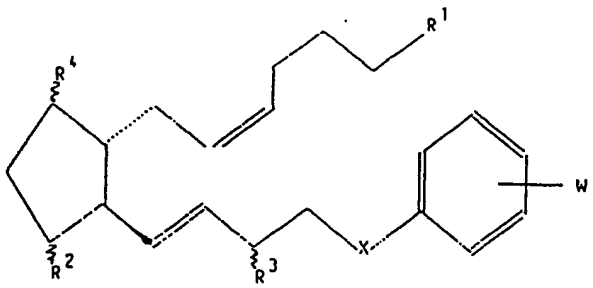
R^5 means methanesulfonyl,

X means oxygen or CH_2,

W means hydrogen or fluorine.

The invention further relates to a process for the production of compounds of formula I, which is characterized in

that a compound of formula II



(II),

in which

R^4 exhibits a hydroxy group and R^1, R^2, R^3, X and W have the above-indicated meanings and free OH groups in R^2, R^3 and W are protected, is reacted with diethylaminosulfur trifluoride [M. Sharma, Tetrahedron Lett. 573 (1977); W. J. Middleton, J. Org. Chem. 40, 574 (1975)] or other fluorinating agents, such as, e.g., $(HF)_n$-pyridine [G. A. Olah, Synthesis 786 (1973)] or SeF_4-pyridine [G. A. Olah, J. Am. Chem. Soc. 96, 925 (1974)] and protected hydroxy groups optionally in R^2, R^3 and W are released and/or free hydroxy groups are esterified, etherified, and/or an esterified carboxy group is saponified or a carboxy group with a physiologically compatible base is converted to a salt or reacted to a clathrate with alpha-, beta- or gamma-cyclodextrin or encapsulated with liposomes.

The reaction of the compounds of general formula II to the compounds of general formula I is performed with diethylaminosulfur trifluoride at -80°C to +40°C, preferably at

$-70^{o}C$ to $+25^{o}C$. As a solvent, dichloromethane, 1.1.2-trifluorotrichloroethane, pyridine, toluene, benzene, ethylene chloride, i.a., preferably toluene and pyridine, are suitable.

The release of functionally modified hydroxy groups R^2, R^3 and W takes place according to the methods known to one skilled in the art. For example, the cleavage of the ether protecting groups is performed in an aqueous solution of an organic acid, such as, e.g., acetic acid, propionic acid, citric acid, i.a., or in an aqueous solution of an inorganic acid, such as, e.g., hydrochloric acid, or in the case of tetrahydropyranyl ethers with use of pyridinium-p-toluene sulfonate, preferably in alcohols as a solvent or with use of anhydrous magnesium bromide, preferably in diethyl ether as a solvent.

To improve the solubility, a water-miscible inert solvent is suitably added with use of aqueous-acid reaction conditions. For example, alcohols, such as methanol and ethanol, ethers, such as dimethoxyethane, dioxane and tetrahydrofuran have proved to be suitable, and tetrahydrofuran is preferably used.

The cleavage of silylether protecting groups takes place, for example, with tetrabutylammonium fluoride according to the methods known to one skilled in the art. As a solvents, for example, tetrahydrofuran, diethyl ether, dioxane, methylene chloride, etc., are suitable. The cleavage is performed preferably at temperatures between 20^{o} and $80^{o}C$.

The saponification of the acyl groups and prostaglandin ester is performed according to the methods known to one skilled

in the art, such as, for example, with basic catalysts, such as, e.g., with alkali or alkaline-earth carbonates or hydroxides in an alcohol or the aqueous solution of an alcohol. As alcohols, aliphatic alcohols, such as, e.g., methanol, ethanol, butanol, etc., but preferably methanol, are suitable. As alkali carbonates and alkali hydroxides, there can be mentioned lithium, sodium and potassium salts. The lithium and potassium salts are preferred. As alkaline-earth carbonates and alkaline-earth hydroxides, for example, calcium carbonate, calcium hydroxide and barium carbonate are suitable. The reaction generally takes place at -10^{o} to $+70^{o}C$, but preferably at $+25^{o}C$.

The introduction of the ester groups CO_2R^4 for R^1 or CO_2R^6 for W, in which R^4 or R^6 represents an alkyl group with 1-10 C atoms, takes place according to the methods known to one skilled in the art. The 1-carboxy compounds (R^4 = H or R^6 = H) are reacted, for example, with diazohydrocarbons in a way known in the art. The esterification with diazohydrocarbons takes place, e.g., in that a solution of the diazohydrocarbon in an inert solvent, preferably in diethyl ether, is mixed with the 1-carboxy compound, dissolved in the same or in another inert solvent, such as, e.g., methylene chloride. After completion of the reaction within 1 to 60 minutes, the solvent is removed and the ester is purified in the usual way. Diazoalkanes are either known or can be produced according to known methods (Org. Reactions, Vol. 8, pages 389-394 (1954)).

The introduction of the ester group CO_2R^4 for R^1 or CO_2R^6 for W, in which R^4 or R^6 represents a substituted or an unsubstituted aryl group, takes place according to the methods known to one skilled in the art. For example, the 1-carboxy compounds are reacted with the corresponding arylhydroxy compounds with dicyclohexylcarbodiimide in the presence of a suitable base, such as, e.g., pyridine, dimethylaminopyridine, triethylamine, in an inert solvent, such as, e.g., methylene chloride, ethylene chloride, chloroform, ethyl acetate, tetrahydrofuran, but preferably with chloroform. The reaction is performed at temperatures between -30^oC and $+50^oC$, preferably at $+10^oC$.

The prostaglandin derivatives of formula I with R^4 or R^6 meaning a hydrogen atom can be converted to salts with suitable amounts of the corresponding inorganic bases with neutralization. For example, by dissolving the corresponding prostaglandin acids in water, which contains stoichiometric amounts of the base, the solid inorganic salt is obtained after evaporation of the water or after the addition of a water-miscible solvent, e.g., alcohol or acetone.

The production of the amine salts takes place in the usual way. For this purpose, the prostaglandin acid is dissolved in a suitable solvent, such as, e.g., ethanol, acetone, diethyl ether or benzene and 1 to 5 equivalents of the respective amine of this solution is added to this solution. In this case, the salt usually accumulates in solid form or is isolated in the usual way after the evaporation of the solvent.

The functional modification of the free hydroxy groups takes place according to the methods known to one skilled in the art. For the introduction of the ester protecting groups, it is reacted, for example, with dihydropyran or methyl vinyl ether in methylene chloride or chloroform with use of catalytic amounts of an acidic condensing agent, such as, e.g., toluenesulfonic acid. The respective enol ether is added in excess, preferably in 1.2 to 10 times the amount of the theoretical requirement. The reaction normally takes place at $-10^{0}C$ to $+30^{0}C$ and is completed after 2 to 45 minutes.

For the introduction of the silylether protecting groups, it is reacted, for example, with t-butyl-diphenylchlorosilane or t-butyl-dimethylchlorosilane in dimethylformamide with use of a base such as, e.g., imidazole. The respective silyl chloride is added in excess, preferably in 1.05 to 4 times the amount of the theoretical requirement. The reaction normally takes place at $0^{0}C$ to $30^{0}C$ and is completed after 1 to 24 hours.

The introduction of the acyl protecting groups takes place by a compound of formula I being reacted in a way known in the art with a carboxylic acid derivative, such as, e.g., acid chloride, acid anhydride, etc.

The new chemically and metabolically stable 9-fluoroprostaglandin derivatives have pharmacological properties which are comparable to those of the unstable thromboxane A_2(TXA_2) or PGH_2. Thus as TXA_2/PGH_2 receptor agonists, they represent a valuable diagnostic instrument for characterizing

prostaglandin receptors or TXA_2/PGH_2 receptor subtypes, with which the importance of the TXA_2/PGH_2-dependent stimulation of platelets and vessels can be established. This applies both for in vitro tests, such as, e.g., receptor characterization or displacement on the receptor, platelet aggregation inhibiting tests, vessel layer constriction, etc, and for pharmacological tests on the animal.

The TXA_2/PGH_2 receptor agonists can be used for specific weakening or elimination of the action of cyclooxygenase inhibitors, of TXA_2-synthetase inhibitors as well as of TXA_2/PGH_2 receptor blockers. Another possibility of use exists in the partial downward adjustment of the TXA_2/PGH_2 action in clinical pictures with increased sensitivity to or production of thromboxane, such as, e.g., those of coronary arteries or vessels with arteriosclerotic lesions.

In combination with a TXA_2/PGH_2 receptor antagonist, the TXA_2/PGH_2 receptor agonist can be used for diagnostic clarification of the involvement of the TXA_2/PGH_2-dependent process in those clinical pictures which require no systemic dose of a TXA_2/PGH_2 receptor agonist for this diagnosis but also in the case of other clinical pictures, provided that undesirable effects of the TXA_2/PGH_2 receptor agonist can be counteracted by an antagonist.

The TXA_2/PGH_2 receptor agonists are further suitable for local control of hemorrhage in the case of defects of the

platelet function, which are based on an impairment of the TXA_2/PGH_2 formation and/or action.

The fluoroprostaglandin derivatives of this invention can also be used in combination, e.g., with beta-blockers, diuretics, phosphodiesterase inhibitors, Ca antagonists or nonsteroidal antiinflammatory agents.

The dose of the compounds is 1-1000 micrograms/kg/per day, if it is administered to the human patient. The unit dose for the pharmaceutically acceptable vehicle is 10 micrograms to 100 micrograms.

For parenteral administration, sterile, injectable aqueous or oily solutions are used. For oral administration, for example, tablets, coated tablets or capsules are suitable. The invention thus also relates to pharmaceutical agents based on compounds of formula I and usual auxiliary agents and vehicles including cyclodextrin clathrates and encapsulation of liposomes.

The active ingredients according to the invention are to be used in combination with the auxiliary agents known and usual in galenicals, for example, for the production of pharmaceutical agents.

EXAMPLE 1

(5Z,9R,13E,15R)-9-Fluoro-15-hydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

The solution of 47 mg (75 micromol) of (5Z,9R,13E,15R)-9-fluoro-15-t-butyl-diphenylsilyloxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester [cf. Dr. U. Klar et al., German patent application, file number P.....] is dissolved in 870 microliters of anhydrous tetrahydrofuran, mixed with 170 microliters of a 1 M tetrabutylammonium fluoride solution in tetrahydrofuran and allowed to stir for three hours under an atmosphere of dry argon. It is poured on ice water, extracted with diethyl ether, rewashed with a saturated sodium chloride solution and dried on magnesium sulfate. The crude oil obtained after removal of the solvent in the water jet vacuum is purified by chromatography on two analytic thin-layer slabs. A mixture of n-hexane and ethyl acetate is used as a mobile solvent, diethyl ether is used as an eluant. 26 mg (67 micromol, 89%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3060, 3030, 3010, 2930, 2870, 1735, 1600, 1585, 1495, 1245, 1040, 970, 750 and 690 cm^{-1}.

EXAMPLE 2

(5Z,9R,13E,15R)-9-Fluoro-15-hydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid:

26 mg (67 micromol) of the compound produced in example 1 is dissolved in 970 microliters of methanol, mixed with 324

microliters of an 8% potassium hydroxide solution and stirred for 5 hours at 25°C. It is poured in ice water, adjusted to a pH of 4 to 5 by adding a saturated citric acid solution, extracted several times with dichloromethane, washed with water and dried on magnesium sulfate. 25 mg (66 micromol, 99%) of the title compound is isolated as a colorless oil.

IR (film): 3600-2400, 3060, 3030, 3010, 2930, 2870, 1710, 1600, 1585, 1495, 1245, 1040, 970, 755 and 690 cm^{-1}.

EXAMPLE 3

(5Z,9R,13E,15S)-9-Fluoro-15-hydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

41 mg (65 micromol) of (5Z,9R,13E,15S)-9-fluoro-15-t-butyl-diphenylsilyloxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester [cf. Dr. U. Klar et al., German patent application, file number P.....] is reacted analogously to example 1 and, after working up and purification, 25 mg (64 micromol, 98%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3060, 3020, 2940, 2870, 1740, 1600, 1590, 1245, 1040, 970, 755 and 695 cm^{-1}.

EXAMPLE 4

(5Z,9R,13E,15S)-9-Fluoro-15-hydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid:

25 mg (64 micromol) of the compound produced in example 3 is reacted analogously to example 2 and, after working up, 24 mg (64 micromol, 100%) of the title compound is isolated as a colorless oil.

IR (film): 3600-2400, 3060, 3010, 2940, 2870, 1710, 1600, 1590, 1500, 1245, 1080, 1040, 970, 755 and 690 cm^{-1}.

EXAMPLE 5

(5Z,9R,11S,13E,15R)-9-Fluoro-11,15-dihydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid:

54 mg (106 micromol) of the compound produced in example 5a is saponified analogously to example 2 and, after working up and purification, 36 mg (92 micromol, 87%) of the title compound is isolated as a colorless oil.

IR (film): 3600-2400, 3090, 3060, 3040, 3010, 2930, 2870, 1710, 1600, 1585, 1495, 1245, 1085, 1040, 975, 755 and 690 cm^{-1}.

a) (5Z,9R,11S,13E,15R)-9-Fluoro-11-benzoyloxy-15-hydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

86 mg (115 micromol) of the compound produced in example 5b is reacted analogously to example 1 and, after working up and purification, 54 mg (106 micromol, 92%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3060, 3020, 2950, 2870, 1735, 1710, 1600, 1495, 1445, 1245, 1110, 1065, 1025, 970, 755, 715 and 695 cm^{-1}.

b) (5Z,9R,11S,13E,15R)-9-Fluoro-11-benzoyloxy-15-t-butyl-diphenylsilyloxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

78 mg (121 micromol) of the compound produced in example 5c is dissolved in 3 ml of anhydrous toluene, mixed with 65 mg of triphenylphosphine, 30 mg of benzoic acid and 39 microliters of azodicarboxylic acid diethyl ester (DEAD). It is stirred for 2.5 hours at 25°C under an atmosphere of dry argon, mixed with water, extracted several times with diethyl ether, dried on magnesium sulfate and the residue obtained after removal of the solvent is purified by chromatography on about 30 ml of fine silica gel. A mixture of ethyl acetate and n-hexane is used as a mobile solvent. 86 mg (115 micromol, 95%) of the title compound is isolated as a colorless oil.

IR (film): 3070, 3020, 3000, 2940, 2860, 1735, 1715, 1600, 1590, 1490, 1445, 1425, 1270, 1245, 1110, 970, 820, 745 and 700 cm^{-1}.

c) (5Z,9R,11R,13E,15R)-9-Fluoro-11-hydroxy-15-t-butyl-diphenylsilyloxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

93 mg (128 micromol) of (5Z,9R,11R,13E,15R)-9-fluoro-11-(tetrahydropyran-2-yloxy)-15-t-butyl-diphenylsilyloxy-16-phenoxy-17,18,19,20-tetranor-5,8(9),13-prostatrienoic acid methyl ester

[cf. Dr. U. Klar et al., German patent application, file number P.....] is dissolved in 2 ml of anhydrous methanol, mixed with 11 mg of pyridinium-p-toluenesulfonate (PPTs) and heated under an atmosphere of dry argon for 2 hours to 55°C. After the cooling, it is mixed with dichloromethane, washed with water and saturated sodium chloride solution, dried on magnesium sulfate and the residue obtained after removal of the solvent is purified by chromatography on four analytic thin-layer slabs. A mixture of n-hexane and ethyl acetate is used as a mobile solvent, ethyl acetate is used as an eluant. 78 mg (121 micromol, 95%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3070, 3030, 3000, 2940, 2850, 1735, 1600, 1590, 1495, 1450, 1245, 1110, 970, 815, 750, 740 and 705 cm^{-1}.

EXAMPLE 6

(5Z,9R,11S,13E,15R)-9-Fluoro-11,15-dihydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

12 mg (31 micromol) of the acid produced in example 5 is dissolved in 0.5 ml of dichloromethane, cooled to 5°C and mixed with an ethereal solution of diazomethane. It is allowed to stir for 15 minutes, excess reagent and solvent are removed by distillation in the water jet vacuum and 12 mg (30 micromol, 97%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3090, 3060, 3030, 3010, 2930, 2870, 1735, 1600, 1590, 1495, 1245, 1085, 1040, 975, 760 and 690 cm^{-1}.

EXAMPLE 7

(5Z,9R,11S,13E,15S)-9-Fluoro-11,15-dihydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid:

139 mg (272 micromol) of (5Z,9R,11S,13E,15S)-9-fluoro-11-benzoyloxy-15-hydroxy-16-phenoxy-17,18,19,20-tetranor-5,8(9),13-prostadienoic acid methyl ester [cf. Dr. U. Klar et al., German patent application, file number P.....] is saponified analogously to example 2 and, after working up and chromatographic purification, 88 mg (224 micromol, 82%) of the title compound is isolated as a colorless oil.

IR (film): 3600-2400, 3070, 3050, 3010, 2940, 2870, 1710, 1600, 1590, 1495, 1445, 1245, 1080, 1040, 980, 755 and 695 cm^{-1}.

EXAMPLE 8

(5Z,9R,11S,13E,15R)-9-Fluoro-11,15-dihydroxy-16-phenoxy-17,18,19,20-tetranor-5,13-prostadienoic acid methyl ester:

16 mg (41 micromol) of the compound produced in example 7 is esterified analogously to example 6 and, after working up and purification, 16 mg (39 micromol, 96%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3070, 3050, 3010, 2940, 2870, 1740, 1600, 1585, 1500, 1245, 1080, 1040, 980, 755 and 695 cm^{-1}.

EXAMPLE 9

(5Z,9R,11S,13E,15R)-9-Fluoro-11,15-dihydroxy-17-phenyl-18,19,20-tri-nor-5,13-prostadienoic acid methyl ester:

360 mg (629 micromol) of (5Z,9R,11R,13E,15R)-9-fluoro-11,15-bis-(tetrahydropyran-2-yloxy)-17-phenyl-18,19,20-tri-nor-5,13-prostadienoic acid methyl ester [cf. Dr. U. Klar et al., German patent application, file number P.....] is mixed with 15 ml of a vinegar/water/tetrahydrofuran (65:35:10) mixture and allowed to stir for 16 hours at 23°C. It is concentrated by evaporation in the water jet vacuum and the residual acetic acid is removed azeotropically by repeated addition of toluene. 238 mg (587 micromol, 93%) of the title compound is isolated as a colorless oil, which is further reacted without purification.

IR (film): 3600-3200, 3070, 3040, 3010, 2940, 2870, 1740, 1600, 1585, 1495, 1245, 1080, 1040, 980, 760 and 695 cm^{-1}.

EXAMPLE 10

(5Z,9R,11R,13E,15R)-9-Fluoro-11,15-dihydroxy-17-phenyl-18,19,20-tri-nor-5,13-prostadienoic acid:

238 mg (587 micromol) of the compound produced in example 9 is reacted analogously to example 2 and, after working up, 176 mg (452 micromol, 77%) of the title compound is isolated as a colorless oil.

IR (KBr); 3600-2400, 3090, 3070, 3030, 3010, 2960, 2930, 2870, 1715, 1605, 1500, 1455, 1410, 1355, 1225, 1205, 1165, 1105, 1085, 1060, 1050, 980, 870, 825, 755 and 700 cm^{-1}.

EXAMPLE 11

(5Z,9R,11R,13E,15S)-9-Fluoro-11,15-dihydroxy-17-phenyl-18,19,20-tri-nor-5,13-prostadienoic acid methyl ester:

314 mg (549 micromol) of (5Z,9R,11R,13E,15S)-9-fluoro-11,15-bis-(tetrahydropyran-2-yloxy)-17-phenyl-18,19,20-tri-nor-5,13-prostadienoic acid methyl ester [cf. Dr. U. Klar et al., German patent application, file number P.....] is reacted analogously to example 9 and, after working up and purification, 221 mg (538 micromol, 98%) of the title compound is isolated as a colorless oil.

IR (film): 3600-3200, 3080, 3060, 3030, 3010, 2940, 2860, 1735, 1600, 1495, 1450, 1410, 1245, 1085, 1045, 970, 750 and 700 cm^{-1}.

EXAMPLE 12

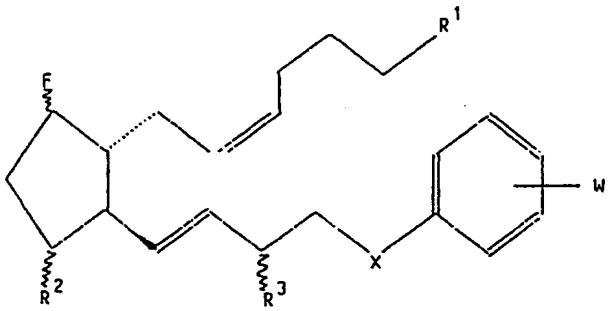
(5Z,9R,11R,13E,15S)-9-Fluoro-11,15-dihydroxy-17-phenyl-18,19,20-tri-nor-5,13-prostadienoic acid:

221 mg (538 micromol) of the compound produced in example 11 is reacted analogously to example 2 and, after working up, 145 mg (372 micromol, 69%) of the title compound is isolated as a colorless oil.

IR (film): 3600-2400, 3080, 3060, 3030, 3010, 2940, 2860, 1710, 1600, 1550, 1495, 1450, 1435, 1410, 1245, 1090, 1045, 1030, 970, 750 and 700 cm^{-1}.

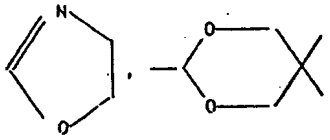
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. 9-Fluoroprostaglandin derivatives of formula I,



(I),

in which

R^1 can be ---  , $COOR^4$, in which R^4 can mean hydrogen or a C_1-C_{10} alkyl radical optionally substituted by halogen, phenyl, C_1-C_4 alkoxy or di-(C_1-C_4) alkylamino, a C_3-C_{10} cycloalkyl radical, a C_7-C_{16} aralkyl radical, a phenacyl radical substituted by W, a C_6-C_{12} aryl radical or a 5- or 6-membered heterocyclic radical with at least one N, O or S atom, or R^1 can be a $CONHR^5$ radical with R^5 meaning hydrogen, C_1-C_{10} alkanoyl or C_1-C_{10} alkanesulfonyl,

R^2 and R^3 each mean a hydrogen atom or a free or functionally modified hydroxy group, and the OH group can be respectively in alpha- or beta-position,

X means a CH_2 group, an O or S atom,

W means hydrogen, $-OR^6$, halogen, -CN-, $-NO_2$, trifluoromethyl or $COOR^6$,

R^6 can be hydrogen, C_1-C_{10} alkyl, C_6-C_{12} aryl or C_7-C_{16} aralkyl substituted by halogen, and, if R^4 means hydrogen, their salts with physiologically compatible bases, as well as the alpha-, beta- or gamma-cyclodextrin clathrates, as well as the compounds of formula I encapsulated with liposomes.

2. 9-Fluoroprostaglandin derivatives of formula I according to claim 1, wherein

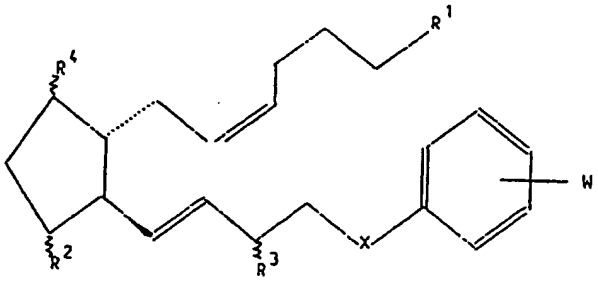
R^1 means the radical $COOR^4$ with R^4 as hydrogen or C_1-C_6 alkyl or R^1 means the radical $CONHR^5$ with R^5 as methylsulfonyl,

X means a CH_2 group or an O atom,

R^2 and R^3 mean hydrogen or hydroxy and

W means hydrogen or fluorine.

3. Process for the production of compounds of formula I, wherein a compound of formula II



(II),

in which

R^4 exhibits a hydroxy group and R^1, R^2, R^3, X and W have the above-indicated meanings and free OH groups in R^2, R^3 and W are

protected, is reacted with diethylaminosulfur trifluoride or other fluorinating agents and protected hydroxy groups in R2, R3 and W are released and/or free hydroxy groups are esterified, etherified, and/or an esterified carboxy group is saponified or a carboxyl group with a physiologically compatible base is converted to a salt or reacted to a clathrate with alpha-, beta- or gamma-cyclodextrin or encapsulated with liposomes.

4. Pharmaceutical agents of one or more compounds according to claim 1 and usual auxiliary agents, vehicles and additives.

5. Use of 9-fluoroprostaglandin derivatives of formula I according to claim 1 as diagnostic auxiliary agents for the characterization of prostaglandin receptors and TXA_2/PGH_2 receptor subtypes.